How to Refine Treatment Choice in Follicular Lymphoma: From Low-Tumor Burden to High-Risk Follicular Lymphoma

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Abstract

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma in the Western world and has an excellent prognosis with current therapies. Management of FL has traditionally included a watch-and-wait approach or chemotherapy. In the past decade, this treatment paradigm has been challenged with the introduction of the anti-CD20 monoclonal antibody rituximab. In FL, numerous treatment options exist, making therapeutic decision-making challenging. Furthermore, given the disease heterogeneity, there is no standard front-line approach. When making therapeutic decisions in FL, it is crucial for practitioners to assess a number of patient-specific factors including age, disease burden, comorbidities, and coping style. In this review, we examine the various front-line treatment options in FL and outline an algorithm for approaching patients with newly diagnosed FL.

Key words: follicular lymphoma, non-Hodgkin lymphoma, rituximab, immunochemotherapy, maintenance

Introduction

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma (NHL) in the Western Hemisphere.[1] With current therapy options, prognosis is favorable, with median overall survival (OS) exceeding 12 years.[2] Recent advances in disease management and our understanding of the biology of FL have led to a dramatic change in the treatment landscape. Despite this progress, FL remains incurable with standard therapies. Therefore, it is critical to design treatment strategies focused on controlling symptoms while considering such factors as age, comorbidities, patient preference, and disease-specific risk factors. Herein, we briefly review the evolving treatment strategies in FL.

Assigning Risk in FL

FL is a heterogeneous disease with varying prognosis based on a combination of clinical, laboratory, and disease parameters. The following metrics have been developed to help guide therapeutic decision-making and determine appropriate candidates for a watch-and-wait (W/W) approach, single agent rituximab, or combination immunochemotherapy.

Tumor Grade

Tumor grade is used to classify FL based on the number of centroblasts per high-power field (HPF). In general, cases harboring a greater number of centroblasts behave more aggressively and are associated with a higher risk of transformation to diffuse large B cell lymphoma (DLBCL). Grade 1 (<5 centroblasts/HPF) and grade 2 (6-15 centroblasts/HPF) FL are combined in the WHO classification given their similar clinical behavior.[3] Grade 3 FL can be further subdivided into 3A and 3B, with the latter distinguished by a lack of centrocytes. Despite a higher tumor grade, FL grade 3A behaves like grade 1-2 FL and as such should be approached in a similar fashion.[4] FL grade 3B represents a distinct entity characterized by a diffuse architectural pattern, frequent loss of CD10 expression, and absence of t(14;18). Consequently, its clinical course and treatment mirror that of DLBCL.[4,5]

Prognostic Index

The Follicular Lymphoma International Prognostic Index (FLIPI) was derived from a cohort of greater than 4000 FL patients diagnosed in the pre-rituximab era and is used to predict OS. The index, as outlined in **Table 1**, stratifies patients into three risk groups, low-risk (0-1 factors), intermediate risk (2 factors), and high risk (≥3 factors) with 10-year OS rates of 71%, 51%, and 36%, respectively. Similarly, the FLIPI-2 score was developed to predict progression-free survival (PFS) in the rituximab era and incorporates five clinical and laboratory parameters including β2-microglobulin.[6] Though these scoring systems aid in determining long-term prognosis, neither provides guidance regarding when to initiate therapy.

Assessing Disease Burden

Assessing tumor burden is important in determining which patients may benefit from W/W versus immediate treatment. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, as outlined in **Table 2**, is frequent-

ly utilized in assessing tumor burden. Patients who harbor 1 or more of the GELF criteria are more likely to require immediate treatment as opposed to a W/W approach.[7]

Approach to the Patient With Newly Diagnosed FL

The diagnosis of FL should be based on an excisional biopsy of an enlarged lymph node, while a core needle biopsy should be reserved for cases without easily accessible disease (eg, retroperitoneal nodes). On histologic evaluation, FL typically displays a nodular growth pattern with obliteration of the nodal architecture. Diagnosing FL based on fine needle aspirate should be discouraged, as this does not provide an adequate sample for assessment of the nodal architecture and tumor grading.

Determining the immunophenotype through either flow cytometry or immunohistochemistry techniques can also aid in the diagnostic evaluation. Classically, FL displays surface immunoglobulin expression and is positive for CD10, CD20, BCL-6, and BCL-2 and lacks CD5 and CD23 expression.[3] FL is characterized by the t(14;18), which results in rearrangement of the immunoglobulin heavy chain on chromosome 14 with the BCL-2 gene on chromosome 18.[8] This translocation leads to overexpression of the BLC-2 gene, which can be detected through conventional cytogenetics, polymerase chain reaction (PCR), or more commonly, fluorescence in situ hybridization (FISH)-based techniques.[3,8]

Following diagnosis, a staging evaluation should be pursued in order to determine the burden of disease. PET/CT imaging is currently recommended to determine both the size and fluorodeoxyglucose (FDG) avidity of nodal and extranodal disease. Furthermore, PET imaging may be helpful in detecting large cell-transformation (LCT) in newly diagnosed patients.[9] A bone marrow biopsy to screen for lymphomatous involvement is also recommended as part of the initial staging workup, though this evaluation may be postponed until therapy is required in those being managed with W/W.[10]

Additionally, blood work including complete blood counts, chemistries, and LDH should be attained at diagnosis and prior to embarking on therapy. Given the risk of reactivation of the hepatitis B virus, screening for hepatitis B surface antigen, and hepatitis B core antibody should also be performed in every patient prior to considering rituximab therapy. In those with positive screening serology, further testing for hepatitis B antigen or hepatitis B viral DNA is appropriate.[11]

When assessing a newly diagnosed FL patient, practitioners must assess disease burden, presence of symptoms attributable to lymphoma, medical co-morbidities, patient preference, and age. An algorithm for approaching newly diagnosed FL patients is depicted in **Table 3**.

Therapy for Symptomatic, High Tumor Burden FL

The addition of rituximab to standard chemotherapy has led to significant improvement in progression-free survival (PFS) and overall survival (OS) versus chemotherapy alone and is considered standard of care.[12,13] Immunochemotherapy options in FL have traditionally included R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), and R-FM (rituximab, fludarabine, and mitoxantrone).[14,15] When these three regimens were compared in a randomized fashion, all

TABLE 1. Follicular Lymphoma International Prognostic Index

Characteristic	Prognostic factor (1 point each)
Age	≥60 years
Stage	Stage III or IV
Hemoglobin	<12 g/dl
Number of nodal sites	>4
Serum LDH	>Upper limit of normal

LDH indicates lactate dehydrogenase

TABLE 2. GELF Criteria

GELF Criteria
☐ Any nodal or extranodal tumor mass ≥7 cm
☐ ≥3 nodal sites, each >3cm
☐ Presence of B symptoms
☐ Splenomegaly
☐ Compression or vital organs compromise
☐ Significant serous effusions
☐ Lymphocyte count >5.0 x 10^9/L
☐ Cytopenias (granulocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)

TABLE 3. Approaches to the Patient with Newly Diagnosed FL

	Low Tumor Burden	High Tumor Burden
Asymptomatic	Watch/Wait versus single-agent rituximab	R-chemo +/- MR versus Watch/Wait
Symptomatic	Single-agent rituximab versus R-chemo	R-chemo +/- MR

MR indicates maintenance rituximab; R-chemo, rituximab-based chemotherapy

three demonstrated a similar OS benefit, and although R-CHOP and R-FM were superior in terms of PFS, R-CHOP was associated with a more favorable safety profile and consequently has frequently been utilized in the frontline setting.[15]

Bendamustine was approved by the FDA in 2008 for the treatment of lymphoid malignancies and has been widely employed in both North America and Europe. In 2013, Rummel and colleagues compared bendamustine plus rituximab (BR) to R-CHOP in front-line FL and showed that BR was associated with both a superior PFS (70 months vs 31 months) and a more favorable toxicity profile compared to R-CHOP.[16] Similarly, in the BRIGHT study, BR was non-inferior to R-CHOP and R-CVP in terms of complete response (CR) rates (31% vs 25%) although BR was associated with a more favorable overall response rate (97% vs 91%). The incidence of nausea/vomiting and allergic reactions was higher in the BR arm, while paresthesias and alopecia were more frequent in the R-CHOP/R-CVP arms. Based on these findings, BR is an attractive alternative to R-CHOP chemotherapy.[17]

Maintenance Therapy in FL

Following induction therapy, patients should undergo a restaging evaluation including repeat PET/CT imaging along with a bone marrow biopsy and aspirate for those with prior bone marrow involvement. Based on restaging studies, patients demonstrating at least a partial response to induction therapy may be candidates for maintenance therapy.

In an effort to prolong remission duration in FL, maintenance therapies have been developed and are frequently utilized. In the phase III PRIMA study, patients with advanced FL achieving a response to induction therapy were randomized to maintenance rituximab (375 mg/m^2 every 8 weeks for 2 years) or observation. With a median follow-up of 3 years, PFS was 75% in the maintenance rituximab (MR) arm compared to 58% in the observation arm. Although OS was not statistically different between the two groups, a higher proportion of patients were in CR in the MR group (72%) compared with observation (52%). MR therapy was associated with an increased incidence of grade 3 and 4 adverse events (24% vs 17%) and grade 2-4 infectious complications (39% vs 24%).[18]

Despite the increased PFS, MR is associated with increased cost, logistical concerns, and some toxicity. Therefore, physicians should have a discussion with patients regarding the risk and benefits of MR therapy.

Management of Asymptomatic, High-Tumor Burden FL

Patients who are asymptomatic with a high-tumor burden are at an increased risk for developing symptoms and potentially end-organ compromise. Therefore, treatment is typically recommended for this population. However, it is important to consider patients who barely qualify as having high-tumor burden, based on the GELF criteria. In this situation, a W/W approach with close monitoring for progression may be appropriate.

In general, therapy for asymptomatic, high-tumor burden FL should mirror that of symptomatic, high-tumor burden FL with rituximab-based chemotherapy followed by MR or observation.

Management of Asymptomatic, Low-Tumor Burden FL

Multiple phase III randomized trials in the pre-rituximab era failed to show an OS benefit for chemotherapy at diagnosis for asymptomatic, low-tumor burden FL.[7,19,20] Given the incurable nature of FL, a conservative approach is favored and a W/W strategy remains a reasonable standard. With this approach, patients are observed for the development of cytopenias, organ compromise, or symptoms attributable to FL.

Two large randomized phase III studies have evaluated single-agent rituximab versus W/W in asymptomatic, low-tumor burden FL. In the study by Ardeshna et al, patients were randomized to W/W, 4 weekly doses of rituximab (rituximab induction), or rituximab induction followed by 2 years of rituximab maintenance. PFS at 3 years was 81% for MR, 60% for rituximab induction, and 33% for the W/W group, although no OS benefit was seen. At 3 years, 46% of W/W patients did not require treatment compared to 88% of patients in the MR group. Compared with the W/W group, those randomized to MR had an improvement in quality of life and experienced less anxiety, although most patients adapted to their illness over time.[21]

In the phase III RESORT trial, patients were treated with 4 weekly doses of rituximab and those who responded were randomized to rituximab every 12 weeks until disease progression, or rituximab re-treatment at progression. Although no difference in time to treatment failure, quality of life, or OS was observed, there was a slight benefit for MR in the time-to-first cytotoxic chemotherapy at 3 years (95% vs 84%), yet this came at the cost of 4.5 times more rituximab.[22]

Based on the lack of an OS benefit, W/W still remains a reasonable standard in this subset of patients. For a minority of patients with significant anxiety and coping issues, rituximab may be beneficial and it is important for practitioners to identify patients falling into this category.

Therapy for Symptomatic, Low-Tumor Burden FL

In symptomatic patients with a low burden of disease, a common presenting complaint is fatigue, and a thorough workup should be pursued to rule out other medical causes. If no other cause for fatigue is ascertained, it is reasonable to try single-agent rituximab to evaluate for improvement in symptoms and disease. In this subset of patients, it is particularly important to consider patient age and comorbidities when weighing treatment options. Elderly patients or those with significant medical comorbidities may be more appropriate candidates for less-intensive single agent-rituximab. Younger, more fit patients would likely benefit from rituximab-based chemotherapy.

Conclusions

Traditionally classified as an indolent disease, FL can present with varying degrees of tumor burden, symptoms, and laboratory abnormalities. Given the disease heterogeneity, there is no uniform standard approach. In symptomatic FL, practitioners must weigh patient age and comorbidities in deciding between single-agent rituximab and rituximab-based chemotherapy. Likewise, in asymptomatic FL, one must balance disease burden and patient preference when deciding between a W/W or treatment approach. Future research efforts should focus on more accurately identifying high-risk patients and evaluating the impact of novel therapies in current treatment paradigms.

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